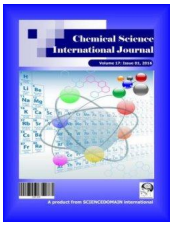

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Synthesis, Characterization and Antibacterial Evaluation of Some Substituted Pyrrolidines

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Series of substituted heterocyclic Chalcones 3-aryl-1-(thiophen-2-yl) prop-2-en-1-one 1-9 had been prepared by using Claisen-Schmidt condensation. In addition, series of substituted Schiff bases N-arylidene benzylamines 10-13 were prepared by the condensation of benzyl amine with various substituted aromatic aldehydes. The reaction of the above materials occurred through 1,3-anionic cycloaddition of azallyl anion of Schiff bases which acted as a nucleophile to the double bond of chalcones afforded the corresponding heterocycles (pyrrolidines 14-24). Spectral data and some physical properties were used to support the structures of the new products. The antibacterial activity of some prepared compounds were tested through its Inhibition effects on two kinds of bacteria.

Keywords: 1,3-anionic cycloaddition; 2-acetyl thiophene; chalcones; Schiff's bases; pyrrolidine; antibacterial activity.

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1. INTRODUCTION

Pyrrolidine ring is found in many natural compounds which possess biological activity such as analgesic potency [1], antimicrobial [2], antibacterial [3], dipeptidyl4 peptidase inhibitors [4], antitumor [5], and histamine H-receptor ligands [6]. Some pyrrolidines also act as potent H3-antagonists [7].

These compounds undergo to typical reactions of secondary or tertiary alkyl amines [8]. Therefore, it can be used as precursors for building other important compounds such as alkaloids and pharmacological active compounds [9-12].

Olefins, such as chalcone [13], maleic anhydride, 2-arylidene-1-tetralone and arylidene malononitrile derivatives were used efficiently as trapping dipolarophiles in high yield and high regio and stereoselectivity [14]. Therefore, the most developed route for the synthesis of these compounds depends on the cycloaddition to an exocyclic bond [15,16].

The 1,3-Anionic cycloaddition provides a way for the synthesis of many heterocycles through the cycloaddition reaction of nonstabilised azomethine yield with the Chalcones [17]. On the synthesis of substituted pyrrolidines, we have examined the 1,3-Anionic cycloaddition reaction of heterochalcones which synthesized from 2-acetyl thiophene 3-aryl-1-(thiophen-2-yl) prop-2-en-1-one with the azomethine yield generated by the treatment of the Schiff bases with sodium hydroxide.

2. EXPERIMENTAL DETAILS

2.1 General

Melting points were determined by Electrothermal 9300 Engineering LTD Apparatus (the melting points are uncorrected), the boiling points were determined by inverting capillary in a thiele tube by using paraffin colorless oil [18]. A Perkin Elmer (lambda 25) UV-VIS-PC spectrophotometer was used for UV measurements. Fourier –Transform Infrared (FT-IR) spectrophotometer (Perkin Elmer model-spectrum one) was used to run IR spectra. The nuclear magnetic resonance (^{1}H-NMR) spectral was performed by using a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer, tetramethyl silane (TMS) as an internal standard, and CDCl3 as a solvent in Yüzüncüyıl University, Turkey.

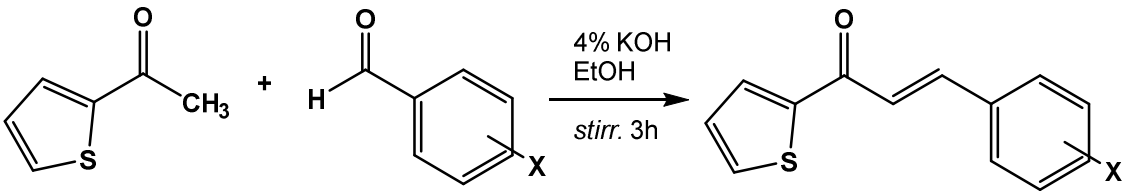
2.2 Synthesis Section

2.2.1 Preparation of Chalcones 1-9 (General procedure) [19]

To an ice cooled mixture of aromatic aldehyde 0.01 mole and 2-acetyl thiophene 0.01 mole in 5 ml of absolute ethanol, add slowly with stirring 10 ml of 4% alcoholic potassium hydroxide solution for 15 min. The stirring was continued for additional 3 h, after completion of addition. The formed precipitate was consequently filtered off, washed with small amount of cold ethanol and recrystallized from ethanol to give the products 1-9. Some physical properties and spectral data were illustrated in the Table 1.

2.2.2 Preparation of Schiff base 10-13 (General procedure) [20]

In a beaker, 100 ml, 0.01 mole of benzylamine, 0.01 mole of aromatic aldehyde and 10 ml of *n*-butanol were heated at 100°C for 10 min. The reaction mixture was cooled and the precipitate was filtered which then recrystallized from ethanol (liquid products was purified by distillation). Some physical properties and spectral data were illustrated in the Table 2.

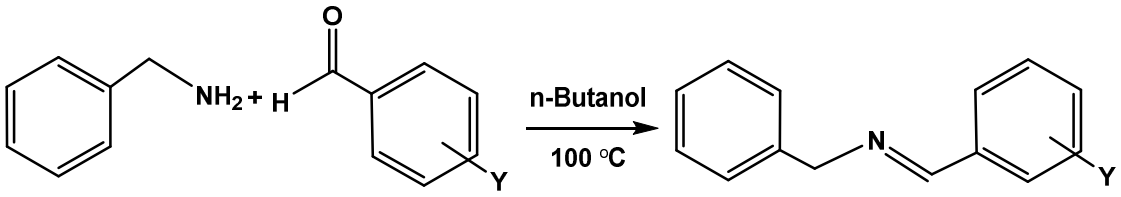


(1-9)

Scheme 1. Preparation of chalcones 1-9

Table 1. Some physical properties and spectral data of chalcones 1-9

Comp. no.	X	m.p. (°C)	Color	Yield (%)	U.V. $CHCl_3\lambda_{max}$ (nm)	FTIR (KBr) $\nu(cm^{-1})$			
						C=O	C=C	C–C	Others
1	H	120-122	Pale yellow	52	292	1650	1599	1572	----
2	2-Cl	119-121	Off-white	94	290	1655	1613	1597	C-Cl 721
3	4-Cl	136-138	Pale yellow	97	331	1648	1599	1589	C-Cl 711
4	3,4-$(OCH_3)_2$	105-106	Yellow	86	363	1639	1586	1573	C-O-C Sym. 1020, Assym. 1264
5	4-OCH_3	88-90	Yellow	77	346	1647	1586	1570	C-O-C Sym. 1030, Assym. 1250
6	4-CH_3	122-125	Off-white	70	336	1646	1588	1566	-----
7	3-NO_2	154-156	Paige	75	307	1650	1598	1572	N–O Sym. 1351, Assym. 1530
8	-furyl	50-52	Pale brown	65	349	1650	1587	1547	C-O-C Sym. 1020, Assym. 1235
9	4-$N(CH_3)_2$	116-118	Orange	46	311	1632	1611	1561	-----



(10-13)

Scheme 2. Preparation of schiff bases (10-13)

Table 2. Some physical properties and spectral data of prepared schiff bases 10-13

Comp. no.	Y	m.p. or b.p*(°C)	Color	Yield (%)	U.V. $CHCl_3\lambda_{max}$ (nm)	FTIR (KBr) $\nu(cm^{-1})$		
						C=N	C–C	Others
10	H	144-118	White	90	281	1625	1596	-----
11	2-Cl	142-143	White	96	273	1639	1583	C-Cl 747
12	4-CH_3	50-52	Pale yellow	88	291	1647	1606	-----
13	-furyl	248-250*	Dark brown	----	283	1646	1602	C-O-C Sym.1014 Assym. 1273

2.2.3 Preparation of pyrrolidines 14-24 (General procedure) [21]

In a 50 ml round-bottomed flask, 0.001 mole of chalcone was dissolved in 10 ml DMSO and 0.001 mole of Schiff base was added. The mixture was magnetically stirred at room temperature for 10 min., then 3 ml of 50% sodium hydroxide solution was added drop wise. The stirring was continued for 3-4 h at room temperature, Icy water was then added to the reaction mixture, the separated precipitates were washed with water until the filtrate became clear and neutral. The solid product was then dried and recrystallized from ethanol to give the products 14-24. Some physical properties and spectral data were illustrated in the Tables 3, 5 and 6.

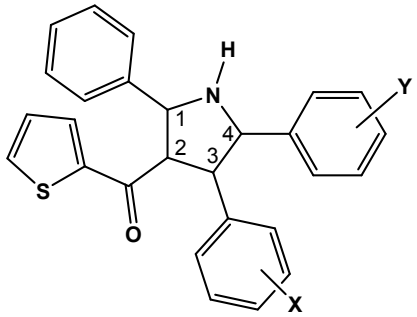
2.3 Preliminary Biological Study

The antibacterial property of certain products against two types of bacterial groups: Gram-negative, *E. coli* and Gram-positive *staphylococcus aureus* were investigated, Table 4.

Of each bacterial species a loopful was cultured in a nutrient broth and incubated at 37°C for 14-16 h, then eventually distributed on the nutrient agar by using a sterile swab. The controls here were Tetracycline, Lincomycine and Nalidixic acid for comparison. The plates were then incubated at 37°C for 18-24 h. Prescott method was used to illustrate the sensitivity of the studied compounds [22]. The results were interpreted according to the report of W.H.O. The resistance R represent the diameter of inhibition zone <11 mm, while the sensitive S was over 16 mm., but moderately sensitive MS was regarded when the inhibition zone is 12-16 mm.

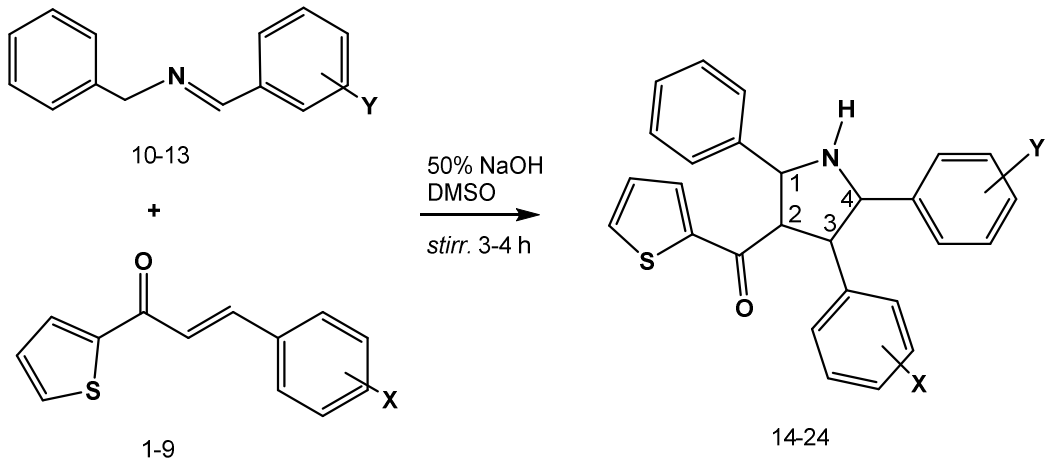
3. RESULTS AND DISCUSSION

Schiff bases [N-Arylidene benzylamine 10-13] were added to 3-phenyl-1-(thiophen-2-yl) prop-2-en-1-one 1-9 via 1,3-anionic cycloaddition under strong basic conditions to afford the corresponding substituted pyrrolidines 14-24. The structures of the synthesized compounds (pyrrolidines) have been confirmed by the spectral methods.



Substituted Pyrrolidines (14-24)

The IR spectra for compounds 14-24 showed strong absorption band in the range of 1635-1652 cm^{-1} related to the stretching vibration of carbonyl groups [23] and a broad absorption band in the range of 3435-3322 cm^{-1} related to the stretching vibration of NH. The FT-IR spectral also manifests absorption bands at 1610-1596 cm^{-1} related to the stretching vibration of the aromatic ring [24,25].



Scheme 3. Preparation of pyrrolidines 14-24

Table 3. Some physical properties of pyrrolidines 14-24

Prod. no.	X	Y	m.p. (°C)	Color	Yield%
14	H	4-CH_3	135-137	Dark paige	87
15	3-NO_2	4-CH_3	121-123	Dark paige	96
16	-furyl	4-CH_3	95-98	Dark brown	88
17	3,4-$(OCH_3)_2$	4-CH_3	80-83	Yellow	92
18	4-Cl	4-CH_3	95-96	Paige	81
19	H	H	143-145	Brown	51
20	-furyl	H	102-105	Dark brown	45
21	4-CH_3	H	40-43	Pale paige	40
22	2-Cl	H	91-93	Pale paige	42
23	4-OCH_3	2-Cl	115-116	Paige	31
24	4-*N*$(CH_3)_2$	2-Cl	133-135	Brown	25

Table 4. Inhibition effect of certain product on growth of *Staphylococcus aureus* and *Escherichia coli*

Compound no.	Test organism			
	E. coli		*Sta. aureus*	
	GIZ in mm.	Mode	GIZ in mm.	Mode
3	18	S	20	S
6	19	S	21	S
8	13	MS	18	S
15	19	S	17	S
17	20	S	12	MS
21	9	R	13	MS
23	7	R	19	S
Control				
Tetracycline	25	S	26	S
Lincomycine	11	R	24	S
Nalidixic acid	22	S	10	R

S = sensitive, MS = moderate sensitive, R= resistant

Table 5. FTIR and U.V. spectral data of pyrrolidines 14-24

Prod. no.	X	Y	U.V. $CHCl_3\lambda_{max}$ (nm)	FTIR (KBr) $\nu(cm^{-1})$		
				C=O	N-H	C⎓C
14	H	4-CH_3	278	1637	3391	1607
15	3-NO_2	4-CH_3	301	1638	3350	1604
16	-furyl	4-CH_3	268	1646	3419	1602
17	3,4-$(OCH_3)_2$	4-CH_3	273	1652	3322	1604
18	4-Cl	4-CH_3	273	1644	3400	1610
19	H	H	284	1643	3411	1596
20	-furyl	H	280	1646	3430	1599
21	4-CH_3	H	272	1642	3411	1599
22	2-Cl	H	277	1645	3401	1599
23	4-OCH_3	2-Cl	274	1640	3435	1606
24	4-*N*$(CH_3)_2$	2-Cl	270	1635	3430	1596

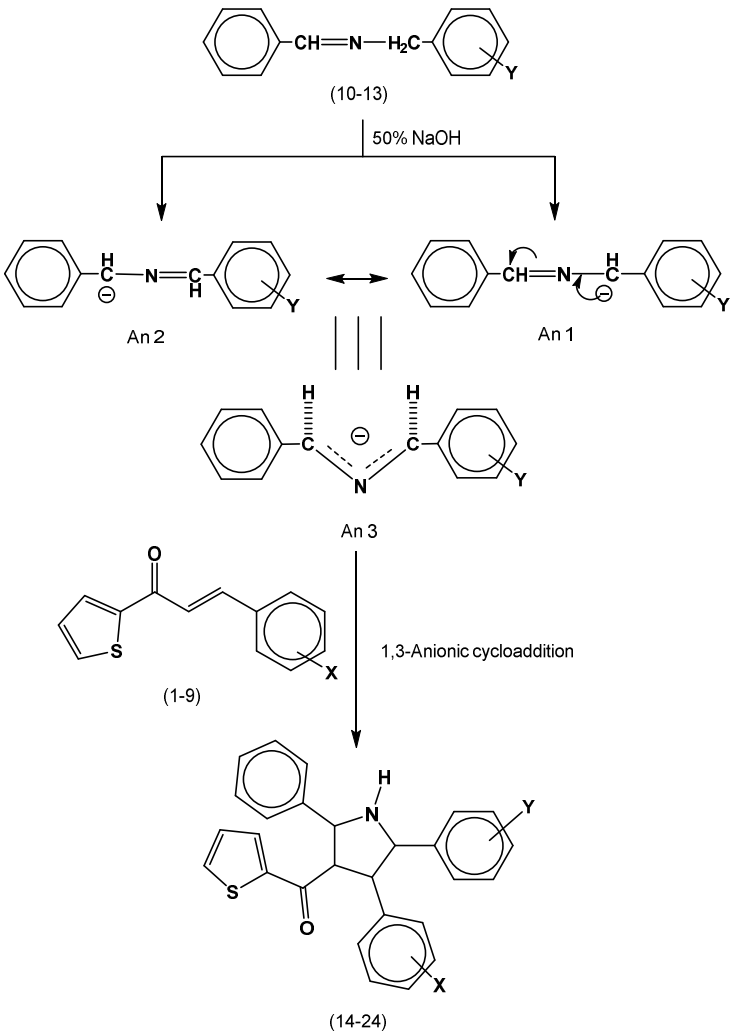
The U.V spectra showed wavelength at maximum absorption (λmax) 301-268 nm which reflects a blue shift with respect to wave length of chalcones at 360-290 nm [26].

The ^{1}H-NMR spectrum of final product 19 (as a representative model in discussing the ^{1}H-NMR spectral data) shows a broad singlet signal resonates at 2.59 ppm (1 H) related to N-H. A doublet signal at 3.03 ppm (1H) was related to the methine proton at C-2, another doublet signal at 3.91 ppm (1 H) was attributed to the methine proton at C-3. A singlet signal showed at 4.63 ppm (1 H) corresponds to the methine proton at C-1 and another singlet signal at 5.2 ppm (1H) due to C-4 proton. The aromatic protons were resonating as multiplet signal at 7.2-8.0 ppm (18 H) [27].

The suggested mechanism for the 1,3-anionic cycloaddition of N-arylidene benzylamine 10-13 to Chalcone 1-9 (as shown in Scheme 4) was initiated by the abstraction of the more acidic proton (benzylic) rather than the olefinic proton. Delocallization of the negative charge of An1 and An2 affording the resonance hybrid An3 which in turn may attack the C=C of Chalcone via 1,3-anionic cycloaddition, which is analogous to the synchronous cycloaddition of 2-azaallyllithium to stilbene [28] to afford final product (substituted Pyrolidine 14-24) with high regiochemical and stereochemical selectivity [29].

Table 6. ^{1}HNMR spectral data of pyrrolidines

Prod. no.	X	Y	Proton of N-H	Proton of C ppm					
				C-1	C-2	C-3	C-4	Ar-H	Others
14	H	4-CH_3	2.69 Broad	4.62 Singlet 1H	3.04 Doublet 1H	3.92 Doublet 1H	5.29 Singlet 1H	7.2-7.9 Multiplet 17H	4-CH3 2.07 Singlet 3H
19	H	H	2.59 Broad	4.63 Singlet 1 H	3.03 Doublet 1 H	3.91 Doublet 1 H	5.2 Singlet 1 H	7.2-8.0 Multiplet 18 H	



Scheme 4. 1,3-Anionic cycloaddition of Schiff bases 10-13 to chalcones 1-9

The preliminary biological study clarified that most of the studied compounds have good antibacterial activity. Compounds 3,6,15 and 17 were sensitive against Escherichia Coli bacteria which represent Gram-negative type. Inhibition of these compounds was similar to that one in Tetracycline and Nalidixic acid and reverse to the effect of the compounds 21 and 23 which were similar to Lincomycine. Compound 8 was a moderately sensitive against this type of bacteria. All these compounds except 17 and 21 have the same inhibition of Tetracycline and Lincomycine which were sensitive against *Staphylococcus aureus* which represent Gram-positive type. Compounds 17 and 21 were moderately sensitive against this type of bacteria.

4. CONCLUSIONS

In conclusion, we have achieved the synthesis of a variety of substituted pyrrolidines through 1,3-dipolar cycloaddition reaction of Schiff bases with heterochalcones (reaction of chalcones derived from 2-acetyl thiophene with Schiff bases via 1,3-cycloaddition had not been reported before) and evaluated their structure by using different spectroscopic techniques. Some of the synthesized compounds showed good antibacterial activity against the bacterial pathogens.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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